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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,331	10/04/2000	Pierre Deslongchamps	6670/OH748	6557

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Darby & Darby PC  
805 Third Avenue  
New York, NY 10022

EXAMINER

EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/679,331	<b>Applicant(s)</b> DESLONGCHAMPS ET AL.	
	<b>Examiner</b> Jon D Epperson	<b>Art Unit</b> 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 August 2004.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 34-36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 34-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of the Application***

1. The Response filed August 12, 2004 is acknowledged.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Status of the Claims***

3. Claims 34-36 were pending. No claims were added or canceled. Therefore, claims 34-36 are currently pending and examined on the merits.

### **Withdrawn Objections/Rejections**

4. All rejections are maintained and the arguments are addressed below.

### **Outstanding Objections and/or Rejections**

#### ***Claims Rejections - 35 U.S.C. 112, first paragraph***

5. Claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for several of the tethered tripeptides that are structurally related to the "RGD" compounds (wherein "R" stands for "arginine", "G" stands for glycine and "D" stands for aspartate) that fall within the broad scope of the claimed invention (see below), is not enabling for the vast majority of compounds that are currently claimed. This is an enablement rejection.

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Any person skilled in the art to which it pertains, or with which it is most nearly connected, would not know how to make and use the claimed invention. Applicants have not provided enough examples of how to use the claimed invention to be enabling for the full breadth of the claims. It is clear from applicant's specification how one might practice this invention with the top two compounds in claim 10 (see original claims, page 53 of specification) because they mimic RGD and it is clear from the specification and known in the literature that these compounds might show similar biological activity to known RGD compounds (see specification, page 11, first paragraph, which teaches a known use in the literature for RGD compounds in cell recognition). However, applicants have not provided sufficient guidance as to how to use any of the other compounds that fall within the broad scope of the claimed invention, which are not related to RGD.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors may include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: Applicant concedes that the breadth of the claims is broad (see specification, page 12, second paragraph) (“the scope of the invention is broad”). Applicant’s formula (1) for a macrocyclic compound in claim 1 reads on an almost unlimited number of compounds because of the enormous number of variable groups that can be independently varied (even for the newly added claims). For example, a variable number of amino acids, non-standard amino acids (e.g.,  $\beta$ -,  $\gamma$ - amino acids), D and L amino acids (note that changes in stereochemistry would also lead to “structures very different from conventional  $\beta$ -turns”), spacer groups, all containing different R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> amino acid side chains (20 total) can be independently varied. Furthermore, different core structures could also be created by using different A1, A2, A3 and T substituents leading to an enormous number of unrelated compounds.

(3 and 5) The state of the prior art and the level of predictability in the art: The therapeutic value for the vast majority of these macrocyclic compounds is not known in the literature. In addition, applicant concedes that these compounds would not be structurally related in form and function (see specification, page 12, second paragraph) (“the compounds ... can adopt structures very different from conventional  $\beta$ -turns, according to the nature of their spacer parts”) (emphasis added). Thus, it is not possible to determine what effect these substitutions and changes in conformation will have on the therapeutic value (if any) of these macrocyclic compounds i.e., the nature of the subject matter is completely unpredictable (e.g., see Parsons et al, conclusion, “The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking

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experimental study”; see also specification page 12, paragraph 2, “the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad”) (emphasis added).

Furthermore, it would be hard to predict what biological target should be used to screen many of these compounds for biological activity and even harder to predict whether or not they would show biological activity (see Parsons et al, conclusion, “The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study”). Even if a biological target was known, the structures of the possible variants are sufficiently diverse that one of ordinary skill would not be able to predict which compounds would be capable of binding to the given biological target (see specification page 12, paragraph 2, “the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad” demonstrating the unpredictable nature of the claimed invention because it reads on many “unrelated” i.e., very different structures). Therefore, the state of the prior art and the level of predictability in the art is quite low.

(4) The level of one of ordinary skill: The level of skill would be high, a person would most likely hold a Ph.D. level degree.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any examples for the vast majority of

compounds that fall within the scope of these broad claims which show their usefulness. Therefore, one of skill in the art would not know how to use the claimed invention (with the exception of the RGD analogs as mentioned above). Furthermore, there is no generic strategy for determining what effect these substitutions and resulting conformational changes will have on the binding affinity and/or selectivity (note: in paper 11, Applicants make only an unsubstantiated claim that all of the newly amended claimed elements would “limit conformational flexibility” presumably to somehow overcome this rejection). In addition, there is no “core” structure from which a biological entity might bind to (i.e., an “XXX” tripeptide is not an “art recognized” binding motif). Applicants’ claims are not limited to any recognizable core structure (i.e., an RGD tri-peptide, which is an “art recognized” binding motif) and, as a result, there can be no common structural motif to which a biological ligand of interest would bind (i.e., Applicants’ claimed XXX structure is not an “art recognized” binding motif). Applicants’ claims also encompass non-natural amino acids (e.g.,  $\beta$ - and  $\gamma$ -), which add yet another layer of unpredictability to the claimed subject matter.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification for all the reasons asserted above does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in using the full scope of the claimed compounds. For example, it is not clear what immediate value a compound of formula (1) would have (referring to claim 34) to the public when the  $A_1$  represents a  $\beta$ - or  $\gamma$ -amino acid with a methyl side chain, the  $A_2$  represents a  $\beta$ -amino acid with an

aromatic ether side chain, A<sub>3</sub> represents a D-amino acid with a methionine side chain, and the tether (T) is -CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>- linker. It would take undue experimentation to determine this value because as applicant concedes the “compounds according to the invention have much flexibility and can adopt structures very different from conventional  $\beta$ -turns, according to the nature of their spacer parts.”

Furthermore, applicant concedes that the vast majority of these compounds are only “potentially” useful in a research setting (see specification, page 19, second paragraph) (“Among the potential uses of the compounds according the present invention are uses in scientific research as research reagents”) and only provides a long “non-specific” list of potential diseases where these macrocyclic compounds “might” some day be useful (see pages 18-19 showing a long non-specific list of potential diseases). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. See also *Brenner v. Manson*, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that “a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.”).

Until some actual and specific significance (i.e., biological activity) can be attributed to the vast majority of Applicants’ claimed compounds, the instant invention is incomplete. In the absence of knowledge of the natural substrate or biological significance for the vast majority of Applicants’ claimed compounds, there is no immediately obvious patentable use for them. Since the majority of the claimed compounds are not supported by either a specific and substantial asserted utility or a well



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established utility for the reasons set forth above, one skilled in the art clearly would not know how to make and use the claimed invention **as broadly as it is claimed**.

Therefore, Applicant's claimed invention is not enabled.

### *Response to Arguments*

6. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... that the specification would enable a person of ordinary skill in the art to make and use the macrocyclic tethered tripeptides recited in claims 34-36. No further information beyond that disclosed in the instant specification would be required by those skilled in the art in order to make and use these compounds" (e.g., see 8/12/04 Response, page 26, third full paragraph).

[2] Applicants argue, "The specification discloses representative examples of the claimed macrocyclic tethered tripeptides (see, for example, pp. 25-27, Tables 1-3; and pp. 35-37, Tables 4-6). These examples constitute a representative cross-section of the compounds called for in the general formulas set forth in claims 34-36" (e.g., see 8/12/04 Response, page 26 last paragraph).

[3] Applicants argue, "Additionally, the specification discloses methods of preparing several of the claimed compounds ..." (e.g., see 8/12/04 Response, page 27, paragraph 1).

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[4] Applicants argue that a patent disclosure “need not enable information within the knowledge of an ordinarily skilled artisan” and cite *Chiron Corp. v. Genetech, Inc.* in support of this position.

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants’ arguments amount to a general allegation that is wholly unsubstantiated because they do not specifically point out how the specification enables a person of skill in the art to make and use the invention as broadly as it is claimed.

[2-3] The Examiner contends that the passages cited by Applicants do not provide “biological activities” for any of the disclosed compounds and, as a result, Applicants’ arguments are moot. As stated in the original rejection, a person of skill in the art would not know how to “use” the vast majority of claimed compounds. The issue is whether or not the enabled embodiment (i.e., the “RGD” analogs) is representative of the scope of the claims. The Examiner contends that they are not because “the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad” demonstrating the unpredictable nature of the claimed invention because it reads on many “unrelated” i.e., very different structures (see specification page 12, paragraph 2; see also Parsons et al, conclusion, “The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* [i.e., the art is unpredictable] but must be determined from case to case by painstaking experimental study”). Thus, a person of skill in the art would NOT expect these dissimilar compounds to behave like the RGD analogs. Therefore, Applicants’ use of the RGD compounds is not “representative” of the claimed scope.

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Furthermore, there is no generic strategy for determining what effect these substitutions and resulting conformational changes will have on the binding affinity and/or selectivity (note: in paper 11, Applicants make only an unsubstantiated claim that all of the newly amended claimed elements would “limit conformational flexibility” presumably to somehow overcome this rejection). In addition, there is no “core” structure from which a biological entity might bind to (i.e., an “XXX” tripeptide is not an “art recognized” binding motif) (emphasis added). Applicants’ claims are not limited to any recognizable core structure (i.e., an RGD tri-peptide, which is an “art recognized” binding motif) and, as a result, there can be no common structural motif to which a biological ligand of interest would bind.

[4] The Examiner contends that the art does not disclose the use for the vast majority of the claimed compounds either (with the exception of the RGD analogs) and Applicants have not provided any evidence to the contrary.

Accordingly, the Enablement rejection cited above is hereby maintained.

### *Conclusion*

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

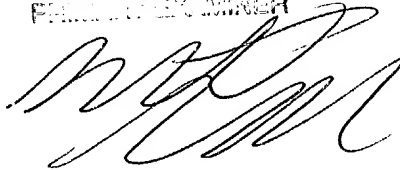
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.

November 3, 2004

DENNITT GELSA  
PATENT EXAMINER

A handwritten signature in black ink, appearing to read 'Jon D. Epperson', is written over the printed name and title of the examiner.